CHEMISTRY LETTERS, pp. 319-322, 1993. © 1993 The Chemical Society of Japan

A Highly Stereoselective Synthesis of α-Glucosides from 1-Thioglucoside Derivative under High Pressure

Yasuo GAMA* and Masahiko YASUMOTO

National Chemical Laboratory for Industry, Tsukuba, Ibaraki 305

High pressure-assisted glycosylation reaction of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with various alcohols by using methyl iodide as an activator gave α-glucosides in good yield with high selectivity without any use of heavy metal salts.

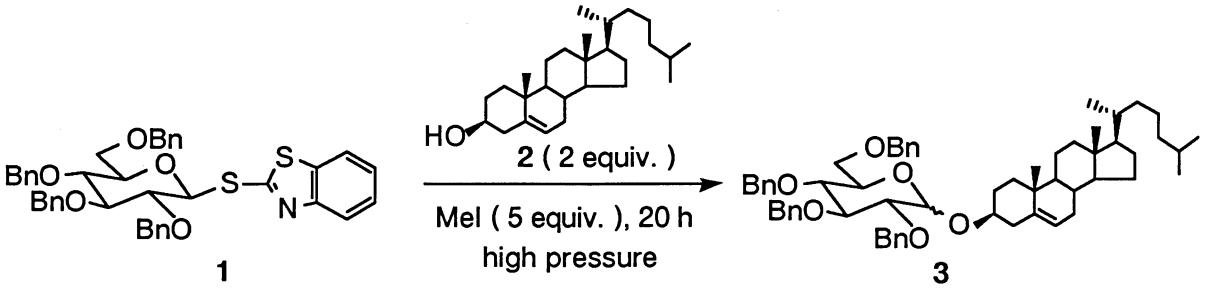
Stereocontrolled construction of *O*-glycoside bond is one of the most challenging problem in carbohydrate chemistry and a large number of methods have been reported.[1] However, there still remains a strong demand to develop simple, mild, and efficient methods for the stereoselective glycosylation. In recent years, it has been reported that several glycosylation reactions under high pressure proceed stereoselectively.[2] We have recently disclosed that the condensation reaction of glycosyl bromide with various alcohols was accelerated under high pressure in the presence of amines to afford α-glucosides in good yield with high selectivity.[3] In this communication, we wish to report the high pressure-assisted glycosylation of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) [4] and various alcohols by using methyl iodide as an activator to give the corresponding glucosides in good yield with high α-selectivity.

We first examined the glycosylation reaction of **1** with cholesterol (**2**) under high pressure by using methyl iodide as an activator in several solvents (Table 1). Treatment of **1** with 2 equivalent of **2** and 5 equivalent of methyl iodide in dichloromethane under 0.8 GPa for 20 h at 50 °C afforded cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**3**) in 51% yield as a mixture of α- and β-anomers (α / β = 89 / 11) along with 3-methylbenzothiazole-2-thione and its salt. When the same reaction was performed under 1.3 GPa for 20 h at 30 °C, the yield increased up to 80% (α / β = 90 / 10). Among several solvents such as dichloromethane, ether, tetrahydrofuran, toluene, and dichlorometane / acetonitrile screened, dichloromethane gave the most favorable results with respect to the yield, but the selectivities were not quite different. The glycosylation

was carried out under atmospheric pressure for 20 h at 30 °C to give a trace amount of **3**.

On the basis of the results, we next undertook the glycosylation of **1** with other alcohols having different reactivities in dichloromethane in the presence of methyl iodide under 1.3 GPa for 20 h at 30 °C. The results are summarized in Table 2. In every case including sterically hindered alcohols, α-glucosides are obtained in good yield with high selectivity. It is assumed that **1** first reacts with methyl iodide under high pressure to afford *N*-methyl quaternary benzothiazolium glucoside.[5] Then, the formed salt reacts with an alcohol to give the corresponding glucoside in a manner similar to 2-pyridyl 1-thioglycosides.[6] A typical procedure is described as follows: A solution of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) (150.4 mg, 0.22 mmol), cholesterol (**2**) (170 mg, 0.44 mmol), and methyl iodide (68 μl, 1.1 mmol) in dry dichloromethane (2 ml) was placed in a sealed Teflon tube. The tube was pressurized at 1.3 GPa in a high pressure equipment[7] and allowed to stand for 20 h at 30 °C. The reaction mixture was depressurized and then purified with column chromatography on silica gel to afford cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-

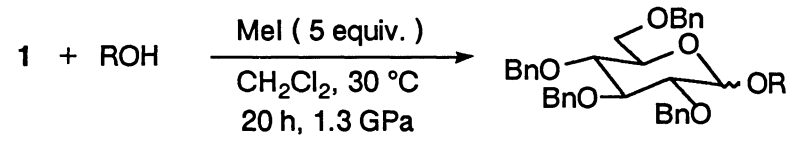
Table 1. Glycosylation reaction of **1** with cholesterol (**2**) under high pressure

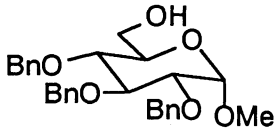
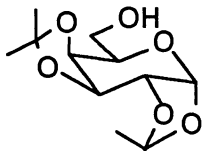
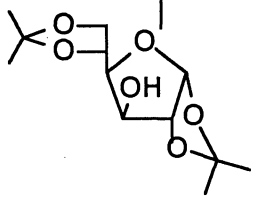


Entry	Solvent	Pressure / GPa	Temp / °C	Yield / % [a]	α / β [b]
1	Et_2O	0.8	50	35	90 / 10
2	THF	0.8	50	30	90 / 10
3	$PhCH_3$	0.8	50	25	89 / 11
4	CH_2Cl_2 / MeCN (3 / 2)	0.8	50	37	89 / 11
5	CH_2Cl_2	0.8	50	51	89 / 11
6	CH_2Cl_2 / MeCN (3 / 2)	1.3	30	49	90 / 10
7	CH_2Cl_2	1.3	30	80	90 / 10
8	CH_2Cl_2	1×10^{-4}	30	trace	—

a) Isolated yield based on **1**. b) The ratio was determined by HPLC analysis.

Table 2. Glycosylation reaction of **1** with various alcohols under 1.3 GPa



Entry	ROH	Yield / % [a]	α / β [b]	δ ^{13}C [c]	
				α-anomer	β-anomer
1	$CH_3(CH_2)_6CH_2OH$	85	89 / 11	96.89	103.68
2	$(CH_3)_3COH$	65	89 / 11	91.50	97.88
3		71	88 / 12	97.25	103.81
4		77	90 / 10	97.05	104.38
5		40	90 / 10	97.99	105.12

a) Isolated yield based on **1**. b) The ratio was determined by HPLC analysis.
c) Chemical shift (δ ppm) in ^{13}C (125 MHz, $CDCl_3$) for the anomeric centers newly formed.

glucopyranoside (**3**) (159 mg, 80% yield). The anomer ratio was determined to be α / β = 90 / 10 by HPLC analysis (Wakosil 5SIL column, 4.0 mm x 300 mm; eluent 10 % ethyl acetate in hexane; UV 254 nm; flow rate 1 ml / min).

In conclusion, we have described the high pressure-assisted glycosylation reaction of 2-benzothiazoyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) with various alcohols by using methyl iodide as an activator affording 1,2-*cis*-glucosides in good yield with high selectivity without any use of heavy metal salts. Further application of this procedure to the synthesis of complex oligosaccharides is now in progress.

References

1) For recent reviews, see : H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, **21**, 155 (1982); R. R. Schmidt,

ibid., **25**, 212 (1986); H. Kunz, *ibid*., **26**, 294 (1987); K. Suzuki and T. Nagasawa, *Yuki Gosei Kagaku Kyokai Shi*, **50**, 378 (1992).

2) For the application of high pressure to glycosylation reactions, see : N. K. Kochetkov, V. M. Zhulin, E. M. Klimov, N. N. Malysheva, Z. G. Makarova, and A. Y. Ott, *Carbohydr. Res*., **164**, 241 (1987); N. K. Kochetkov, V. M. Zhulin, N. M. Malysheva, E. M. Klimov, and Z. G. Makarova, *ibid*., **167**, C8 (1987); W. G. Dauben and P. Köhler, *ibid*., **203**, 47 (1990).

3) M. Sasaki, Y. Gama, M. Yasumoto, and Y. Ishigami, *Tetrahedron Lett*., **31**, 6549 (1990).

4) Thioglucoside **1** has already been used as a glycosyl donor and activated by copper (II) triflate to give α-glucosides in good yield with good selectivity, see : T. Mukaiyama, T. Nakatsuda, and S. Shoda, *Chem. Lett*., **1979**, 487.

5) It is well known that the Menschutkin reaction effectively proceeds under high pressure, see : K. Matsumoto, A. Sera, and T. Uchida, *Synthesis*, **1985**, 1.

6) H. B. Mereyala and G. V. Reddy, *Tetrahedron*, **47**, 6435 (1991).

7) A description of the high pressure equipment employed in this study has been given previously, see : M. Kurabayashi, K. Yanagiya, and M. Yasumoto, *Bull. Chem. Soc. Jpn*., **44**, 3413 (1971); M. Yasumoto, N. Asou, Y. Taguchi, T. Tsuchiya, I. Shibuya, and K. Yonemoto, *J. Natl. Chem. Lab. Ind*., **86**, 163 (1991).

(Received November 10, 1992)